PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2770PTWO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP02/04303	International filing date *(day/month/year)* 18.04.2002	Priority date *(day/month/year)* 18.04.2001
International Patent Classification (IPC) or both national classification and IPC A61K31/4725		
Applicant ISTITUTO SUPERIORE DI SANITA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.11.2002	29.07.2003
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Allnutt, S Telephone No. +49 89 2399-7817

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP02/04303

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-54 as originally filed

Claims, Numbers

1-26 filed with the letter of 18.12.2002

Drawings, Sheets

1/34-34/34 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 27

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to th report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-4, 13, 14-26 (partially-Industrial Applicability)

   because:

   ☒ the said international application, or the said claims Nos. 14-26 relate to the following subject matter whicl does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-4, 13-18 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opini could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide a amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, accordinç Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10,24
	No:	Claims	1-9,11-23,25-26
Inventive step (IS)	Yes:	Claims	
	No:	Claims	10,24
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	14-26

2. Citations and explanations

   see separate sheet

Item III

1. Claims 14-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. The attention of the applicant is drawn to the fact that for the present application only an incomplete search has been carried out, and that a clarity objection has been raised in connection with claims 1,3-5,15-26 (see sheet PCT/ISA/210, and in particular the last paragraph). The Examining Division agrees with the clarity objections raised by the Search Division. The search was carried out limiting to the diseases as defined in claims 9 and 23. The examination has been carried out accordingly.
Claims 1-4, 13-18 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. In particular, the wording "blocking the migration/invasion of cells (claim 1, 15)..; obtained through inhibition or modulation of molecules and proteolytic enzymes (claim 3, 17)...; for modulating biological processes (claim 13);..involving cell migration and invasion, tissue infiltration (claims 13 and 14); " cannot be considered as defined, real treatments of a pathological condition.
The description and further dependent claims give concrete examples of possible diseases associated with these mechanisms (eg. inflammatory, autoimmune and neoplastic disorders (claim 5)). However, the scope of claims 1-4,13-18 is not limited to the treatment of said conditions, but embraces an undefined number of other conditions all allegedly capable of being improved or prevented by the above mentioned mechanisms. As a result of this, the skilled person is unable to establish the scope of claims 1-4,13-18, which therefore have to be considered as unclear.

3. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 00 33654 A (UNIV MARYLAND BIOTECH INST) 15 June 2000 (2000-06-15) cited in the application
D2: CONANT M A: 'REDUCTION OF KAPOSI'S SACROMA LESIONS FOLLOWING TREATMENT OF AIDS WITH RITONOVIR' AIDS, LONDON, GB, vol. 11, no. 10, August 1997 (1997-08), pages 1300-1301, XP000983605 ISSN: 0269-9370
D3: WO 99 63998 A (GROETTRUP MARCUS ;ZINKERNAGEL ROLF (CH); INST NAT SANTE RECH MED () 16 December 1999 (1999-12-16)

D4: BERTHELOT P ET AL: 'Dramatic cutaneous psoriasis improvement in a patient with the human immunodeficiency virus treated with 2',3'-dideoxy,3'-thyacytidine [correction of 2',3'-dideoxycytidine] and ritonavir [letter] [published erratum appears in Arch Dermatol 1998 Apr;134(4):452]' ARCHIVES OF DERMATOLOGY, XX, XX, vol. 133, no. 4, 1 April 1997 (1997-04-01), page 531,452 XP002095182 ISSN: 0003-987X

D5: ANDRE ET AL: 'An inhibitor of HIV-1 protease modulates proteasome activity, antigen presentation, and T cell responses' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 95, no. 22, 1 October 1998 (1998-10-01), pages 13120-13124, XP002095181 ISSN: 0027-8424

D6: SGADARI C; BARILLARI G; TOSCHI E; ET AL: 'HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of Kaposi sarcoma' NATURE MEDICINE, vol. 8, no. 3, March 2002 (2002-03), pages 225-232, XP002214286

The documents considered in the present processing are consecutively numbered D1-D6; this numbering results from the citations D1-D6 found in the Search Report (SR) of the corresponding PCT application. It will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

Item V

Novelty

1. The subject matter of claims 5-9,11,12,19-23, 25,26 are anticipated by prior art document D1 and therefore do not fulfill the requirements of Art 33(2) PCT.

D1 discloses the use of HIV protease inhibitors for treating a variety of diseases such as cancer, inflammation, ischaemia and autoimmune disorders and the mechansisms associated therewith.

D2 discloses reduction of kaposi's sarcoma following ritonavir administration. It further discusses inhibition of a KS-associated herpesvirus protease.

D3 describes treating inflammation, autoimmune diseases, diabetes, cancer, scleroses, psoriasis and rheumatoid arthritis with ritonavir or saquinavir (1-2000 mg).

D4 discloses the use of ritonavir for treating psoriasis (1200 mg/day).

D5 discloses the treatment of autoimmune diseases and proteasome inhibitory activity with ritonavir.

The remaining claims 10 and 24 are considered to be formally novel (Art 33(2) PCT).

Inventive Step

2. Claims 10 and 24 are not considered as involving an inventive step (Article 33(3) PCT).

The closest prior art is considered to be D1 disclosing the use of HIV-protease inhibitors for treating various disorders.

The difference of the application with respect to the closest state of the art D1 is the use of HIV-protease inhibitors **in association** with anti-inflammatory, antiangiogenic or anti-tumor drugs.

The applicant claims the combination can be used to treat a variety of disorders already disclosed in D1.

The technical problem may be formulated as "how to provide an alternative method of treating various disorders given in claims 9 and 23"

There is no teaching within D1 or prior art documents D2-D6 that HIV-protease inhibitors may be effective for treating e.g. tumors, retinopathy, psoriasis when used in combination with anti-inflammatory, antiangiogenic or anti-tumor drugs.

However, there appears to no evidence by way of experimental data in the description to support claims 10 and 24.

Therefore the problem is not considered to be solved and the criteria for inventive step according to Article 33(3) PCT is not fulfilled.

Further Remarks:

3. Industrial Applicability (Art 33(4) PCT).

For the assessment of the present claims 13-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Article 64.1 PCT

4.Although D6 is not a valid prior art document pursuant to Art 64.1 PCT, it discloses all the features of claims 5-7, 9, 11-12, 19-21, 23 and 25-26.

CLAIMS - Art. 19PCT

1. Use of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI, for the preparation of a medicament for treating a subject suffering from or susceptible to a condition which can be treated or prevented by blocking the migration/invasion of cells selected in the group of: endothelial, neoplastic, inflammatory or immune cells.
2. Use according to claim 1 wherein cell migration/invasion results in tissue infiltration and/or oedema formation.
3. Use according to claims 1-2 wherein the block is obtained through inhibition or modulation of molecules and proteolytic enzymes selected in the group of: MMPs including MMP-2, stromelysins and matrilysin; enzymes activating MMPs; thrombospondin; bFGF and VEGF alone or associated between them, Tat alone or in the presence of bFGF.
4. Use according to claim 3 in which the proteolytic enzymes are MMPs.
5. Use according to claims 1-4 wherein the condition to be treated or prevented is at least one of the following pathologies: inflammatory, autoimmune, neoplastic, non-neoplastic angioproliferative diseases.
6. Use according to claims 1-6 wherein the HIV-PI has an anti-angiogenic, anti-tumour, anti-oedemigenic and/or anti-inflammatory activity for the treatment of KS, tumours and non-neoplastic angioproliferative, inflammatory and autoimmune diseases.
7. Use according to claims 1-6 wherein the HIV-PI is selected among the following compounds: indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, lopinavir and ritonavir, corresponding pharmaceutically acceptable derivatives and chemical analogues, and mixtures thereof.
8. Use according to claim 7 wherein the compounds are administered at the following doses: indinavir: 600 mg/day, 1200 mg/day, 2400 mg/day and 4800 mg/day; saquinavir: 900 mg/day; 1800 mg/day, 3600 mg/day, 7200 mg/day
9. Use according to claims 1-8 wherein the pathological condition is selected in the group of: Kaposi's sarcoma, angiogenesis; non-neoplastic angioproliferative diseases of eye, kidney, vascular system, skin, such as, for example, diabetic retinopathy, retrolental fibroplasia, trachoma, vascular

glaucoma, psoriasis, immune and non-immune inflammation, atherosclerosis, keloids; benign and malignant tumours of the soft tissues, the cartilages, the bones and the blood; autoimmune diseases in general, in particular systemic lupus erythematosus, scleroderma, rheumatoid arthritis, psoriasis, thyroiditis, ulcerous rectocolitis and Crohn's disease, Goodpasture's syndrome, systemic vasculitis, Sjögren's syndrome, primitive biliary cirrhosis; inflammatory diseases, in particular chronic inflammation associated with allergies and with viral infective, bacterial or parasitic agents, including the Castleman's multicentric disease.

10. Use according to claim 9 wherein the HIV-PI is in association with anti-inflammatory, anti-angiogenic or anti-tumour drugs.

11. Use according to claims 1-10 in subjects infected or not infected by HIV.

12. Use according to claims 1-11 wherein the drug is administered according to a procedure selected among; oral, intravenous, intramuscular, subcutaneous, intradermal, intraperitoneal, intrathecal, intrapleural, intrauterine, transmucosal, rectal, vaginal, intralesional or percutaneous administration.

13. Method for modulating biological processes involving cell migration and invasion, tissue infiltration and activity of molecules involved in these cell pathways, including MMPs and thrombospondin, said method comprising the administration of an effective amount of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI.

14. Method for treating pathological conditions involving cell migration and invasion, tissue infiltration and activity of molecules involved in these cell pathways, including MMPs and thrombospondin, said method comprising the administration of a therapeutically effective amount of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI.

15. Method for treating a subject suffering from or susceptible to a condition which can be treated or prevented by blocking the migration/invasion of cells selected in the group of: endothelial, neoplastic, inflammatory or immune cells, said method comprising the administration of a therapeutically effective amount of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI.

16. Method according to claim 15 wherein cell migration/invasion results in tissue infiltration and/or oedema formation.

17. Method according to claim 15 wherein the block is obtained through inhibition or modulation of molecules and proteolytic enzymes selected in the group of: MMPs including MMP-2, stromelysins and matrilysin; enzymes activating MMPs; thrombospondin; bFGF and VEGF alone or associated between them, Tat alone or in the presence of bFGF.

18. Method according to claim 17 wherein the proteolytic enzymes are MMPs.

19. Method according to claim 15 wherein the condition to be treated or prevented is at least one of the following pathologies: inflammatory, autoimmune, neoplastic, non-neoplastic angioproliferative diseases.

20. Method according to claim 15 wherein the HIV-PI has an anti-angiogenic, anti-tumour, anti-oedemigenic and/or anti-inflammatory activity for the treatment of KS, tumours and non-neoplastic angioproliferative, inflammatory and autoimmune diseases.

21. Method according to claim 15 wherein the HIV-PI is selected among the following compounds: indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, lopinavir and ritonavir, corresponding pharmaceutically acceptable derivatives and chemical analogues, and mixtures thereof.

22. Method according to claim 21 wherein the compounds are administered at the following doses: indinavir: 600 mg/day, 1200 mg/day, 2400 mg/day and 4800 mg/day; saquinavir: 900 mg/day; 1800 mg/day, 3600 mg/day, 7200 mg/day

23. Method according to claim 15 wherein the pathological condition is selected in the group of: Kaposi's sarcoma, angiogenesis; non-neoplastic angioproliferative diseases of eye, kidney, vascular system, skin, such as, for example, diabetic retinopathy, retrolental fibroplasia, trachoma, vascular glaucoma, psoriasis, immune and non-immune inflammation, atherosclerosis, keloids; benign and malignant tumours of the soft tissues, the cartilages, the bones and the blood; autoimmune diseases in general, in particular systemic lupus erythematosus, scleroderma, rheumatoid arthritis, psoriasis, thyroiditis, ulcerous rectocolitis and Crohn's disease, Goodpasture's syndrome, systemic vasculitis, Sjögren's syndrome, primitive biliary cirrhosis; inflammatory

diseases, in particular chronic inflammation associated with allergies and with viral infective, bacterial or parasitic agents, including the Castleman's multicentric disease.

24. Method according to claim 15 wherein the HIV-PI is in association with anti-inflammatory, anti-angiogenic or anti-tumour drugs.

25. Method according to claim 15 wherein the subjects are subjects infected or not infected by HIV.

26. Method according to claim 15 wherein the drug is administered according to a procedure selected among; oral, intravenous, intramuscular, subcutaneous, intradermal, intraperitoneal, intrathecal, intrapleural, intrauterine, transmucosal, rectal, vaginal, intralesional or percutaneous administration.

Box No. VIII (iv) DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America)

The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (iv). If this Box is not used, this sheet should not be included in the request.

Declaration of inventorship (Rules 4.17(iv) and 51*bis*.1(a)(iv)) for the purposes of the designation of the United States of America:

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This declaration is directed to international application No. PCT/..... (if furnishing declaration pursuant to Rule 26*ter*).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: Italy - No. RM2001A000210 of April 18, 2001

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name: Barbara ENSOLI

Residence: Via Monte Pollino, 2- 00141 ROME - ITALY
(city and either US state, if applicable, or country)

Mailing Address: as above

Citizenship: Italian

Inventor's Signature: Barbara Ensoli
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date: April 11, 2002
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name:

Residence:
(city and either US state, if applicable, or country)

Mailing Address:

Citizenship:

Inventor's Signature:
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date:
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iv)".

See Notes to the request form